Occupational exposures and uncontrolled adult-onset asthma in the ECRHS II

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ABSTRACT

Occupational exposure is a well-recognized modifiable risk factor for asthma but the relationship between occupational exposure and asthma control has not been studied. We aimed to study this association among working-age adults from the European Community Respiratory Health Survey (ECRHS).

Data were available for 7077 participants (in average 43 years, 45% never smokers; 5867 without asthma, 1210 with current asthma). Associations between occupational exposure to specific asthmagens and asthma control status (33% with uncontrolled asthma, based on the GINA guidelines) were evaluated using logistic and multinomial regressions, adjusted for age, gender and smoking status, with study areas included as a random effect.

Statistically significant positive associations were observed between uncontrolled adult-onset asthma and both past 12-month and 10-year exposure to any occupational asthmagens (odds ratio (OR) [95% confidence interval]: 1.6[1.0-2.4], 1.7[1.2-2.5], respectively), high (1.7[1.0-2.8], 1.9[1.3-2.9]) and low (1.6[1.0-2.7], 1.8[1.2-2.7]) molecular weight agents, and cleaning agents (2.0[1.1-3.6], 2.3[1.4-3.6]), with stronger associations for long-term exposures. These associations were mainly explained by the exacerbation domain of asthma control and no associations were observed between asthmagens and partly-controlled asthma.

These findings suggest that occupational exposure to asthmagens is associated with uncontrolled adult-onset asthma. Occupational risk factors should be quickly identified to prevent uncontrolled asthma.

Studying asthma from a population-based perspective allows a better understanding of the determinants of clinical disease manifestations, including occupational risk factors[1-3]. Despite the importance of the separate concepts of asthma severity, which reflects the intrinsic severity of the disease, and asthma control, which reflects the activity of the disease over a short period, the terminology applied is often used interchangeably and is not standardized[4]. Asthma severity is difficult to define in epidemiology[4, 5] and the definitions used are not always adequate[3]. Recent guidelines have moved away from the concept of severity to focus more on asthma control[3, 4].

Studies on asthma control have mainly been conducted in clinical studies and few epidemiologic studies in large populations have assessed asthma control in a comprehensive manner. Multidimensional scales following Global Initiative for Asthma (GINA) guidelines have been applied to define asthma control in epidemiology in both the European Community Respiratory Health Survey (ECRHS) and the French Epidemiological study on the Genetic and Environment of Asthma (EGEA) surveys[6-10]. This measure of asthma control in a categorical scale, combining diurnal and nocturnal respiratory symptoms, asthma attacks, activity limitations, lung function and exacerbations, has not been formally validated. However, the classification of asthma control evaluated through GINA expert opinions in clinical settings was similar to scores from specific control questionnaires[11, 12]. Epidemiological results also support the validity of such a control scale[7]. Few epidemiological studies have evaluated the environmental risk factors of asthma control[6, 8]. For example, domestic exposures to products in spray form and air pollution have been found to be associated with poorly-controlled asthma[6, 9].

Occupational exposure to asthmagens, which included more than 350 agents specifically identified as disease-related, is a modifiable asthma risk factor implicated in as much as 15% of adult-onset asthma [1]. Work-related asthma is commonly classified as occupational asthma caused by exposure to agents at work (appeared in adulthood) or work-aggravated pre-existing asthma [2]. In the EGEA survey[5], a strong association was found between occupational exposure to asthmagens and asthma severity in adult-onset asthma. Asthma exacerbation due to work is beginning to receive increased attention[2]. The role of occupational exposures in uncontrolled adult-onset asthma, as assessed through various dimensions of the disease reflecting both acute and chronic activity of the disease, has not been studied.

Based on well-characterized available data in ECRHS for both asthma control[10] and occupational exposure to asthmagens[13], the main objective of the present analysis was to investigate associations between past 12-month and past 10-year occupational exposure to specific asthmagens, including both high- and low-molecular weight sensitizing agents and irritants, and adult-onset uncontrolled asthma.

METHODS

Study design

The ECRHS is a multicentre general population study (http://www.ecrhs.org/). The baseline study (ECRHSI) was conducted from 1991 to 1993 as previously described[14, 15]. Briefly, a random sample of individuals aged 20 to 44 years was contacted to complete a short screening questionnaire on respiratory symptoms. In a second step, both a 20% random sample of the entire group and a respiratory symptom-enriched sub-group (online supplement) were invited to complete a second detailed questionnaire and to undergo a clinical examination (lung function tests including spirometry and a non-specific bronchial reactivity test).

Participants from ECRHSI, from 29 centres in 14 countries, were invited to a follow-up survey (ECRHSII), conducted between 1998 to 2002, and to complete a face-to-face questionnaire (precise information on asthma, respiratory symptoms, and occupational history) and a clinical examination (lung function tests, blood samples)[13, 16]. The information collected included age, smoking status (never, former or current smoker), body mass index (overweight: BMI$\geq$25 kg/m²), use of inhaled corticosteroids, asthma control, and sensitization to common allergens (online supplement). Sensitization to common allergens was defined as a specific serum Immunoglobuline E (IgE) antibodies, to at least one out of four common allergen (house dust mite, cat, timothy grass or *Cladosporium herbarum*), at concentration of at least 0.35 U/mL. According to baseline forced expiratory volume in the first second (FEV_1) based on Quanjer et al. reference values[17], participants were classified as 'with' (< 80% of predicted values) or 'without' low FEV_1. Bronchial hyper-reactivity (BHR) was defined as a reduction in maximum FEV_1 of at least 20% of its postsaline value for a methacholine dose of 1 mg or less. The overall response rate for the follow-up participation was approximately 65%. This analysis was limited to participants in ECRHSII from the 26 study centres in 12 countries[10, 13]. The information was used to evaluate both asthma control and occupational exposure among participants ever employed and with available data for sex, age, smoking habits, current asthma (n=9019). After excluding 1942 participants, 796 from the enriched sample (all individuals without current asthma) and 1146 from the random sample (with past asthma (n=167) or without current asthma but with asthma symptoms or treatment in ECRHSII (n=979)), analysis was performed on 7077 participants (1210 with 'current asthma'; 5867 with 'never asthma', Figure 1).

Asthma

Participants from the random sample were classified as 'never asthma' (n=5867) if they never reported doctor-diagnosed asthma (never at ECRHSI and ECRHSII), or any current asthma-like symptoms (wheezing or whistling without a cold, woken by an attack of shortness of breath), and did not use asthma medications in ECRHSII. Participants were classified as 'current asthma' at follow-up (n=1210), using previous definitions[10, 18], if they had reported doctor-diagnosed asthma, and if in the last 12 months, they had reported

respiratory symptoms (wheezing, nocturnal chest tightness, attack of breathlessness following activity, at rest or at night time, at least one asthma attack) or had used asthma medications in ECRHSII. As previously described by Cazzoletti et al[10], participants with 'current asthma' were classified as: (i) 'Controlled asthma' if all the following features were present: diurnal symptoms less than once a week, no nocturnal symptoms, no asthma attacks, short-acting β2-agonists twice or less per week in the past 3 months; no activity (work, other activities) limitations and no use of oral steroids in the past 12 months, and FEV1 ≥ 80% predicted. (ii) 'Partly-controlled asthma' when 1 or 2 of the above features of control were absent. (iii) 'Uncontrolled asthma' when asthma, shortness of breath or wheezing had caused hospital/emergency admissions in the past 12 months; or oral corticosteroids were used on short courses or continuously in the past 12 months; or the subject had more than 12 asthma attacks (>1/week) in the past 3 months; or > 3 of the above features were absent (detailed in the online supplement).

We defined adult-onset asthma as first onset occurring at age 16 or above (see online supplement). For analyses including age of onset, 91 participants were excluded due to missing values or inconsistent responses for the two surveys for this variable.

Occupational exposure assessment

Both past 12-month and 10-year occupational exposures to 22 exposures (18 categories of asthmagens classified at high risk for asthma and four categories of *a priori* 'non-asthmagenic' agents[5] classified at low risk for asthma; online supplement) were assigned through the application of an asthma-specific Job-Exposure Matrix (JEM)[19] followed by an expert re-evaluation step, as described elsewhere[13]. This classification of 'non-asthmagenic' agents[5] may be discussed especially for possible exposure to irritants. Associations between occupational exposures and asthma control were studied for exposure to (i) any asthmagens, (ii) each of the three large groups of asthmagens (high molecular weight (HMW), low molecular weight (LMW) agents, mixed exposure or irritant peaks), (iii) specific asthmagens when at least 5% of participants were exposed (latex, highly reactive chemicals and industrial cleaning chemicals), and (iv) 'non-asthmagenic' agents only (non-exposed to asthmagens), with participants classified as non-exposed as the referent category.

Strategy of analysis

Specific hypotheses have been tested: (1) uncontrolled asthma is associated with occupational exposure to asthmagens, including exposure to HMW, LMW agents and cleaning agents, but not to *a priori* defined non-asthmagenic agents[5, 19] ; (2) these associations are expected for adult-onset asthma but unexpected for childhood-onset asthma[5]. Additional analyses were performed to assess the association between occupational exposure and each of the four asthma control domains (lung function, symptoms, exacerbations, activity limitations)[6, 8] and without including the exacerbation domain in the asthma control definition. To check the

consistency of our main reported results, analyses were stratified by BMI, smoking habits, gender, and sensitization to common allergens, as previously suggested[13, 20].

Associations between occupational exposure and asthma control were tested using a multinomial logistic regression. Participants without any history of asthma served as the referent category with controlled, partly controlled, and uncontrolled asthma being the nominal outcome category. All associations with p-value $\leq$ 0.05 were deemed statistically significant. Potential heterogeneity among areas (English-speaking (UK and USA), Northern, Centre or Southern areas in Europe) was evaluated using the Q statistic. All analyses were adjusted for age, gender and smoking status with area included as a random effect[21]. Other additional analyses are described in the online supplement.

RESULTS

Participants were on average 43 years old, 45% were never smokers, and 17% had current asthma (Table E1, online supplement). More women than men reported current asthma especially for adult-onset asthma ($p<0.001$). Women were more likely to be exposed to occupational asthmagens than men (21.1% *vs* 13.4% in the past 12 months, respectively; Table E1) and especially to cleaning agents (8.8% *vs* 0.8%, respectively; $p<0.001$) while men were more exposed to non-asthmagenic products. Among participants with current asthma, those with childhood-onset asthma were on average younger, with a higher education level, were less often current smokers, and had a higher prevalence of sensitization to common allergens and bronchial hyper-reactivity than those with adult-onset asthma. Among participants with adult-onset asthma, 30% and 40% had uncontrolled and partly-controlled asthma, respectively (Table 1). According to the control definition, participants with exacerbations were always classified as uncontrolled and those with uncontrolled asthma more often used corticosteroids and had more symptoms. Similar trends were observed for childhood-onset asthma (Table E2).

For childhood-onset asthma, no associations were observed between asthma control and both past 12-month and 10-year occupational exposure, with ORs lower than one (Table 2; Table E3).

For adult-onset asthma, statistically significant associations were observed between past 12-month occupational exposure to any asthmagens, for HMW and LMW asthmagens and cleaning agents, and uncontrolled asthma (Table 2). Results were very similar after adjustment for 'pets at home' or for sensitization to common allergens (not shown). We performed an additional analysis stratified by inhaled corticosteroid (ICS) used. The magnitude of the association between past 12-month asthmagen exposure and uncontrolled asthma was similar when considering ICS users (1.6[1.0-2.8]) and non-users (1.4[0.7-2.9]). No association was observed for other specific asthmagens or for *a priori* 'non-asthmagenic' irritants (at low risk for asthma) and uncontrolled adult asthma (Table 2).

Analyses performed between past 10-year occupational exposure and adult-onset asthma control showed stronger associations (Table 3). No significant heterogeneity was observed when we performed a meta-analysis by area (Figure 2). Nonetheless, the association between past 10-year occupational exposure to

asthmagens and uncontrolled asthma was stronger in three geographic areas (English-speaking, Northern and Central Europe). Similar trends were observed for past 12-month occupational exposure to asthmagens (not shown). Higher ORs were observed between occupational exposure to HMW and cleaning agents and uncontrolled adult-onset asthma among normal weight participants and among non-smokers (Figure E1). ORs were similar in men and women for exposure to HMW agents but for LMW agents, including industrial cleaning agents, significant associations were observed only in women. Regarding sensitization to common allergens (Figure E1), a higher OR was observed in sensitized participants for exposure to HMW agents and in non-sensitized participants for exposure to LMW agents including industrial cleaning agents. Similar trends were observed for past 12-month occupational exposures (not shown).

When studying the association between occupational exposure and each domain of adult-onset asthma control separately, significant associations were observed only for the 'exacerbations' domain (Table 4). In addition, 12-month exposure to HMW agents was significantly associated with adult-onset asthma treated with oral corticosteroids (2.7[1.1-6.3]) and the ORs were 1.8[0.8-4.0], 0.6[0.1-2.6], 1.1[0.2-4.8] for asthmagens, LMW and industrial cleaning agents, respectively. Further analyses were conducted without including the exacerbation domain in the asthma control definition ('current clinical control' domain; Table 3). Lower ORs were observed with non-significant associations for 12-month occupational exposure, whereas significant associations were observed for 10-year occupational exposure and uncontrolled asthma for each asthmagens.

Population attributable risk (PAR) for uncontrolled adult-onset asthma for 12-month exposure to asthmagens was 9.4%.

DISCUSSION

Our study shows that occupational exposure to asthmagens is associated with uncontrolled adult-onset asthma in a large population-based study. The associations were stronger for long-term than for current occupational exposures. The observed associations with uncontrolled asthma were mainly explained by the exacerbations domain of asthma control. Our results suggest that both exposure to sensitizers and irritants are associated with uncontrolled asthma and exacerbations. The population attributable risk of uncontrolled asthma due to past 12-month occupational exposure was found to be 9%, approximately half of the PAR for adult-onset asthma overall[1].

The strengths of our study are the 3-level asthma control scale used, which was assessed in a comprehensive manner by integrating several dimensions of the disease, and the assessment of occupational exposure to asthmagens with an asthma-specific JEM. Other strengths are the specificity of the results, the absence of association with *a priori* 'non-asthmagenic' agents and strong associations for asthmagens with adult-onset asthma.

In ECRHS II, significant associations were found between occupational exposure to dusts, gases and fumes in general (evaluated by the ALOHA JEM) and severe asthma exacerbation[21]. In the present analysis we evaluated occupational exposure to specific asthmagens by an asthma-specific JEM combined with an expert review step[19,13]. Re-evaluation by an expert blinded to disease status ensures the objectiveness of the method. To limit misclassification errors specificity was favoured, a job was classified as exposed to asthmagen only if the probability to be exposed was high for an important number of subjects in that job[19]. There is no evidence for recall bias in job history[22] but we are not aware of misclassification errors especially for 10-year exposure. This approach is less prone to bias than self-reported exposures[23] and gives reliable estimates of exposure to asthmagen[5, 13, 19]. The Asthma-specific JEM was designed to evaluate exposure to agents causing asthma and may be less appropriate to evaluate exposure to agents aggravating asthma. However, exposures classified at low risk for asthma might be risk factors involved in work-aggravated asthma. In the present analysis, we studied work-related asthma as we cannot distinguish between these two entities (occupational or work-aggravated asthma). The lack of association for childhood-onset asthma, with ORs lower than one, is consistent with the healthy hire worker effect[24]. Furthermore, a recent study suggested that individuals with childhood-onset asthma tend to have a higher education level than those without asthma[25], a finding also observed in our study. As a consequence, those individuals might be less exposed in adulthood which is consistent with our findings.

Stronger associations were observed for past 10-year than for past 12-month occupational exposures for adult-onset uncontrolled asthma, a finding consistent with one report in EGEA studying long-term exposure to air pollution[6]. This phenomenon might be due to the fact that persistent exposures to asthmagens may directly induce uncontrolled asthma or a more severe form of the disease[5, 26]. In EGEA, occupational exposure to asthmagens was associated with severe adult-onset asthma but not with mild asthma[5]. Asthma

remission is very low in adults, and if the remission does not occur a few years after the onset, the disease tends to become chronic[27, 28]. Current adult-onset asthma is related to disability[29]. Most workers who are removed from exposure to the causal agent maintain persistent symptoms and bronchial hyperresponsiveness[26]. The prognosis of occupational asthma is improved by early and complete removal from exposure[30]. Therefore, work-related asthma might be more often uncontrolled due to the persistence of exposures. Participants with uncontrolled asthma might be less currently at work or exposed, because activity limitation was used to evaluate uncontrolled disease. Investigating 10-year occupational exposure reduces this bias but does not entirely eliminate it unless only participants working during the follow-up are studied. Therefore, our results might be underestimated.

We investigate for the first time uncontrolled asthma following GINA guidelines (2006-2010) in association with occupational exposures. However, it could be argued that findings from EGEA may reflect a relationship between occupational exposure and "uncontrolled asthma" rather than severity, due to limited information regarding asthma activity and treatments in EGEA[5]. In EGEA, cases were recruited from chest clinics and asthma may be 'more severe' than in a general population. Consistent results were observed in both surveys but ORs were much higher with large confidence intervals in EGEA[5]. In ECRHS, few subjects were exposed to specific hazards that might have been of interest (flour, diisocyanantes (< 1% of subjects exposed)) which is a limitation of our analysis. For exposure to cleaning agents, our results are consistent with those observed between domestic exposure to cleaning sprays and poorly-controlled asthma[9].

Contrary to associations observed between quality of life or air pollution and asthma control[6, 7], the association observed between asthmagens and partly-controlled asthma was not 'in-between' those observed with controlled asthma and with uncontrolled asthma. The hypothesis for this absence of trend for asthma control is that the association observed for uncontrolled asthma was mainly due to exacerbations which are not part of the definition of partly-controlled asthma. Asthma control consists of two main domains: (i) lack of impairment (absence of symptoms, minimal treatment use, normal activity level and lung function level), and (ii) lack of future risk to the patient (absence of asthma exacerbations, prevention of accelerated decline in lung function over time and no side-effects from medications)[4, 11]. It has been suggested that exacerbations should be considered separately from current clinical control because they may occur even if the patient has adequate current control of symptoms and few activity limitations[4]. Asthma exacerbation due to work has not been widely reported, however this might be a key problem in occupational settings[2]. Our definition of exacerbation includes hospital/emergency admissions and the use of oral corticosteroids on short courses or continuously in the past 12 months[10]. Oral corticosteroid used continuously may also be considered as a marker of asthma severity. In previous studies, exacerbations were defined only by hospitalization or emergency aspects[31] or in addition to the 'use of oral corticosteroids when needed' to evaluate severe exacerbations[21]. In ECRHS both aspects of exacerbations seem to be linked to occupational exposure to asthmagens[21]. More work is needed regarding the standardization of the definition of asthma exacerbations in epidemiological studies.

Another strength of our analysis is the consistency of our findings. The association between occupational exposure and uncontrolled asthma was not modified by gender, smoking habits, BMI or sensitization to common allergens, although stronger associations were observed in non-smokers and in females. Exposure to LMW agents more than doubled the risk of uncontrolled asthma among participants without sensitization, while exposure to HMW agents doubled the risk among those with sensitization. These results are consistent with a previous report[32]. Our results suggest that overweight participants are not more susceptible to occupational exposures than those with lower BMI, as previously suggested with air pollution[6]. Associations between occupational exposure to asthmagens and uncontrolled asthma seem to be mainly driven by three geographic areas (English speaking (UK, US), Northern and Central Europe), which might partly be due to the heterogeneity of the prevalence of uncontrolled asthma across Europe[10] or to regional differences in occupational exposures, medication practices, or other unmeasured correlates of geographic area.

The study has potential limitations (a cross sectional study; centres not representative of the country) as previously discussed[10]. Asthma control may be difficult to define in epidemiology, although the validity of such control scale was supported by epidemiological results[7, 10]. Although all associations between asthmagens (known risk factors for asthma) and uncontrolled asthma were studied according to *a priori* hypotheses[5, 6, 8, 13], it may be argued that our results regarding specific asthmagens require cautious interpretation due to multiple testing[33].

Our study suggests a strong deleterious effect of occupational exposure to asthmagens in uncontrolled adult-onset asthma. These results are consistent with the hypothesis that occupational exposure to asthmagens can quickly induce uncontrolled asthma[5]. We observed no association with partly-controlled asthma, which is consistent with previous results on asthma severity[5]. Both exposures to low- and high-molecular weights agents and to cleaning agents seem related to uncontrolled asthma. Occupational exposure is a preventable risk factor and the importance of prevention was recently underlined[21, 30, 34]. Preventing asthma exacerbations, an important asthma control domain[4, 11], is essential since severe asthma exacerbations have been related to accelerated decline in lung function[2]. Furthermore, uncontrolled asthma is associated with poorer health-related quality of life[7]. It is important to identify potential occupational risk factors quickly and reduce these exposures as soon as possible to prevent uncontrolled asthma.

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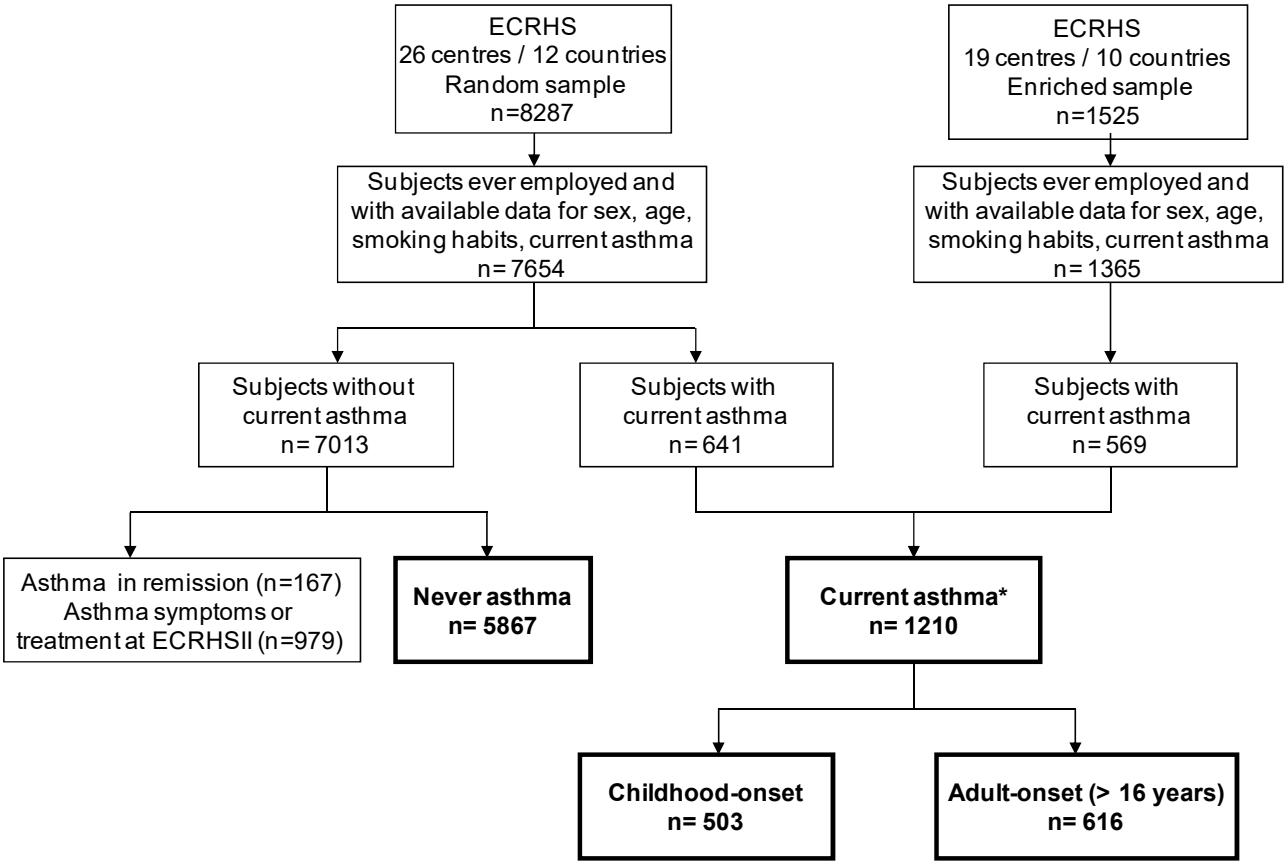
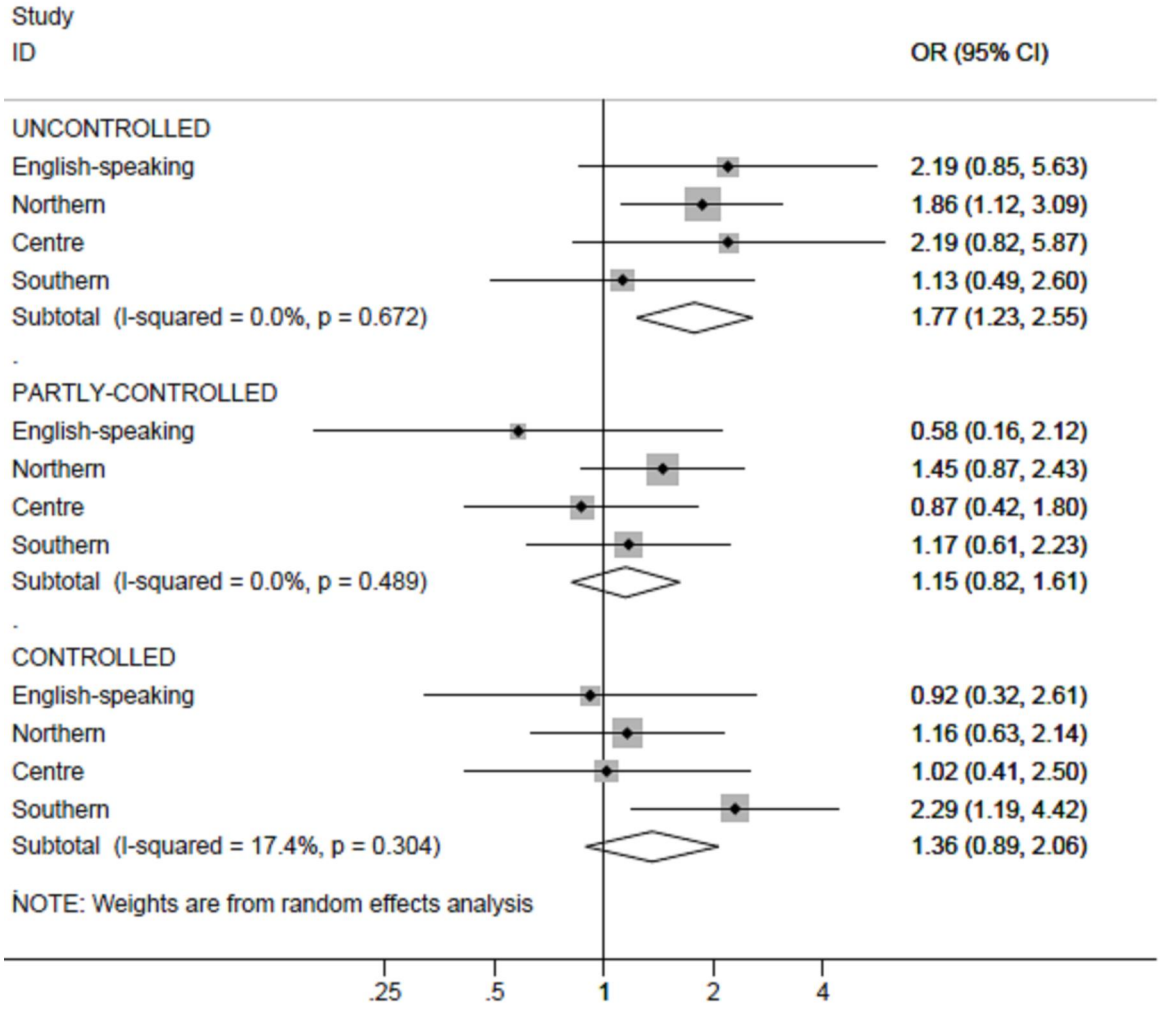
Figure 1: Flow chart of selected population in ECRHS II survey



* 91 missing values for age of asthma onset

Figure 2. Results from meta-analysis by geographical areas – 10-year exposure



Adjusted for age, sex, smoking habits, country (random effect); Reference: participants with 'never asthma' Participants exposed to non-asthmagenic agents or exposed to asthmagens were compared to non-exposed participants

Table 1-Description of ECRHS II population with asthma according to adult-onset asthma control

	Controlled asthma n=167	Partly controlled n=217	Uncontrolled asthma n=161	p value
Women,%	68.3	65.4	67.7	ns
Age, mean (SD)	43.5 (6.9)	43.9 (7.1)	44.6 (6.5)	ns
Sensitization to common allergens	n=153 56.2	n=188 50.0	n=138 44.9	ns
Total IgE > 100 kU/L, %	n=153 37.3	n=188 38.3	n=138 44.9	ns
BHR, %	n=122 32.8	n=131 51.9	n=73 65.8	<0.001
Used of inhaled corticosteroids, last 12 mths %	n=166 25.9	n=212 47.2	n=158 66.5	< 0.001
Oral corticosteroids, past 12 months#	0.0	3.7	23.5	< 0.001
Four domains of asthma control, %	n=167	n=217	n=161	
Lung function (Quanjer), FEV1 < 80%	0.0	20.6	22.5	< 0.001
Symptoms, past 3 months	0.0	54.8	86.3	< 0.001
Exacerbations, past 12 months	0.0	0.0	35.4	< 0.001
Activity limitation, past 12 months	0.0	24.0	52.8	< 0.001
Smoking habits, %	n=167	n=217	n=161	ns
Non-smokers	45.5	46.1	46.6	
Ex-smokers	24.0	27.2	27.9	
Current smokers	30.5	26.7	25.5	
Age finishing full-time education , %	n=167	n=217	n=161	ns
< 17 years old	26.4	25.3	26.7	
17 – 20	34.7	27.7	29.2	
> 20	38.9	47.0	44.1	
Body mass index, mean (SD),%	n=166	n=200	n=140	ns
< 25 kg/m^2	45.8	45.0	38.6	
25-30 kg/m^2	37.9	36.5	36.4	
≥ 30 kg/m^2	16.3	18.5	25.0	
"Have you had to leave jobs (during follow-up) because it affected your breathing?"	n=163 3.7	n=212 6.6	n=152 14.5	0.001
Asthma-specific job exposure matrix, %	n=167	n=216	n=161	ns
Non-asthmagenic irritants, in life	15.6	13.9	16.8	
Asthmagens, in life	26.4	23.2	31.1	

* Out of 616 participants with adult-onset asthma, 545 were classified as controlled, partly or uncontrolled asthma (n=71 missing values for asthma control)

use of oral corticosteroids 'when needed', 'continuously', 'in short courses'(see Question 3, annex 1)

As previously described by Cazzoletti et al[10], participants with 'current asthma' were classified as 'Controlled asthma': all the following features were present: diurnal symptoms <1/week, no nocturnal symptoms, no asthma attacks, short-acting β2-agonists ≤2/ week in the past 3 months; no activity (work, other activities) limitations and no use of oral steroids in the past 12 months, and FEV1 ≥ 80% predicted

'Partly-controlled asthma':1 or 2 of the above features were absent.

'Uncontrolled asthma'*:* asthma, shortness of breath or wheezing had caused hospital/emergency admissions in the past 12 months; or oral corticosteroids were used on short courses or continuously in the past 12 months; or the subject had more than 12 asthma attacks (>1/week) in the past 3 months; or > 3 of the above features were absent.

Sensitization to common allergens was defined as a specific serum Immunoglobuline E antibodies to at least one out of four common inhalant allergen (house dust mite, cat, timothy grass or *Cladosporium herbarum*) at concentrations of 0.35 U/mL or more.

According to baseline forced expiratory volume in the first second (FEV_1) based on Quanjer et al. reference values[17], participants were classified as 'with' (< 80% of predicted values) or 'without' low FEV_1.

Bronchial hyper-reactivity (BHR) was defined as a reduction in maximum FEV_1 of at least 20% of its postsaline value for a methacholine dose of 1 mg or less

Table 2 – Relationship between 12-month occupational exposure and asthma control in ECRHS II population

	Childhood-onset Asthma, OR [95% IC]*				**Adult-onset Asthma,** OR [95% IC]*			
	Exposed never/ C/P/U asthma, n	Controlled Asthma	Partly controlled Asthma	Uncontrolled Asthma	Exposed never/ C/P/U asthma, n	Controlled Asthma	Partly controlled Asthma	Uncontrolled Asthma
Never asthma /Current asthma, n		5344/128	5344/128	5344/127		5344/143	5344/187	5344/125
Asthma JEM *								
Asthmagens, any	910/ 17/17/19	0.8 [0.4-1.3]	0.8 [0.4-1.3]	0.8 [0.5-1.4]	910/ 30/35/34	1.1 [0.7-1.6]	0.9 [0.6-1.3]	**1.6 [1.0-2.4]**
HMW asthmagen, any	471/8/8/12	0.7 [0.3-1.5]	0.7 [0.3-1.4]	1.0 [0.5-1.8]	471/17/20/21	1.0 [0.6-1.8]	0.9 [0.5-1.4]	**1.7 [1.0-2.8]**
Latex	328/5/4/7	0.7 [0.3-1.8]	0.5 [0.2-1.3]	0.8 [0.4-1.8]	328/12/12/13	1.0 [0.5-1.9]	0.7 [0.4-1.3]	1.4 [0.7-2.6]
LMW asthmagen, any	567/12/8/12	0.9 [0.5-1.6]	0.6 [0.3-1.2]	0.8 [0.5-1.6]	567/21/17/23	1.1 [0.7-1.9]	0.7 [0.4-1.1]	**1.6 [1.0-2.7]**
Highly reactive chemicals	278/7/5/5	1.0 [0.4-2.1]	0.7 [0.3-1.6]	0.6 [0.3-1.6]	278/12/8/12	1.3 [0.7-2.4]	0.6 [0.3-1.2]	1.6 [0.9-3.1]
Cleaning agents	243/5/3/4	0.9 [0.4-2.4]	0.5 [0.2-1.6]	0.7 [0.2-1.9]	243/12/13/15	1.2 [0.6-2.2]	0.9 [0.5-1.7]	**2.0 [1.1-3.6]**
Mixed environment	217/4/5/5	0.6 [0.2-1.7]	0.8 [0.3-2.1]	0.8 [0.3-2.1]	217/4/8/6	0.8 [0.3-2.2]	1.1 [0.5-2.2]	1.5 [0.6-3.4]
Non- asthmagens	920/23/25/22	0.9 [0.6-1.5]	1.0 [0.6-1.6]	0.9[0.6-1.5]	920/25/25/20	1.2 [0.8-2.0]	0.8 [0.5-1.3]	1.3 [0.7-2.2]

Nominal logistic regressions adjusted for age, sex, smoking habits, country (random effect)

Reference: participants with 'never asthma'

* Participants exposed to asthmagens or exposed to non-asthmagenic agents were compared to non-exposed participants. HMW: high molecular weight; LMW: low molecular weight agents.

C: controlled asthma; P: partly controlled asthma; U: uncontrolled asthma

As previously described by Cazzoletti et al[10], participants with 'current asthma' were classified as 'Controlled asthma': all the following features were present: diurnal symptoms <1/week, no nocturnal symptoms, no asthma attacks, short-acting β2-agonists ≤2/ week in the past 3 months; no activity (work, other activities) limitations and no use of oral steroids in the past 12 months, and FEV1 ≥ 80% predicted

'Partly-controlled asthma':1 or 2 of the above features were absent.

'Uncontrolled asthma'*:* asthma, shortness of breath or wheezing had caused hospital/emergency admissions in the past 12 months; or oral corticosteroids were used on short courses or continuously in the past 12 months; or the subject had more than 12 asthma attacks (>1/week) in the past 3 months; or > 3 of the above features were absent.

Table 3 – Relationship between occupational exposure to asthmagens and adult-onset asthma control

	12-month occupational exposure, Asthma JEM*					10-year occupational exposure, Asthma JEM*				
	All A/HMW/LMW/C Exposed, n	Asthmagen, all	HMW, any	LMW, any	Cleaning agents	All A/HMW/LMW/C Exposed, n	Asthmagen all	HMW, any	LMW, any	Cleaning agents
Never asthma (reference)	4424 910/471/567/243	1.0	1.0	1.0	1.0	4771 1172/607/748/345	1.0	1.0	1.0	1.0
Asthma control										
Controlled	122 30/17/21/12	1.1 [0.7-1.6]	1.0 [0.6-1.8]	1.1 [0.7-1.9]	1.2 [0.6-2.2]	141 44/23/34/21	1.2 [0.8-1.8]	1.1 [0.7-1.8]	1.4 [0.9-2.1]	1.5 [0.9-2.5]
Partly control.	168 35/20/17/13	0.9 [0.6-1.3]	0.9 [0.5-1.4]	0.7 [0.4-1.1]	0.9 [0.5-1.7]	186 50/30/27/24	1.0 [0.7-1.4]	1.1 [0.7-1.6]	0.8 [0.5-1.2]	1.3 [0.8-2.0]
Uncontrolled	107 34/21/23/15	**1.6** **[1.0-2.4]**	**1.7** **[1.0-2.8]**	**1.6** **[1.0-2.7]**	**2.0** **[1.1-3.6]**	134 50/33/35/26	**1.7** **[1.2-2.5]**	**1.9** **[1.3-2.9]**	**1.8** **[1.2-2.7]**	**2.3** **[1.4-3.6]**
Current clinical control of asthma (exacerbations not taken into account)										
Controlled	125 32/18/22/13	1.1 [0.7-1.7]	1.1 [0.6-1.8]	1.2 [0.7-1.9]	1.3 [0.7-2.3]	144 46/25/35/22	1.3 [0.9-1.8]	1.2 [0.8-1.9]	1.4 [1.0-2.2]	**1.6** **[1.0-2.6]**
Partly control.	179 41/26//19/15	1.0 [0.7-1.4]	1.1 [0.7-1.7]	0.7 [0.4-1.1]	1.0 [0.6-1.8]	200 57/37/30/27	1.1 [0.8-1.5]	1.2 [0.9-1.8]	0.9 [0.6-1.3]	1.4 [0.9-2.1]
Uncontrolled	90 25/14/19/11	1.3 [0.8-2.1]	1.3 [0.7-2.3]	1.5 [0.9-2.6]	1.6 [0.8-3.1]	111 39/23/29/20	**1.6** **[1.1-2.3]**	**1.6** **[1.0-2.6]**	**1.8** **[1.1-2.7]**	**2.1** **[1.2-3.5]**

Multinomial logistic regressions adjusted for age, sex, smoking habits, country (random effect)

Reference: participants with 'never asthma'

To allow the comparison of all results between adult-onset asthma control and clinical control of asthma in a same table, associations between 12-month exposure to asthmagens and adult-onset asthma control (above on the right) are reported twice (both in Tables 2 & 3).

* Participants exposed to asthmagens were compared to non-exposed participants (participants exposed to non-asthmagens excluded).

'Current clinical control' domain was defined as previously (Table 2) for ***'Controlled asthma'*** and ***'Partly-controlled asthma'*** whereas participants with 'current asthma' were classified as ***'Uncontrolled asthma'*** only when the participant had more than 12 asthma attacks (>1/week) in the past 3 months; or > 3 of the above features were absent (exacerbations not taken into account to defined uncontrolled asthma).

A: asthmagens; HMW: high molecular weight agents; LMW: low molecular weight agents; C: Cleaning agents

Table 4 - Occupational exposure to asthmagens and adult-onset asthma according to four dimensions of asthma control

	12-month occupational exposure, Asthma JEM*				10-year occupational exposure, Asthma JEM*			
	Asthmagen, any	HMW, any	LMW, any	Cleaning agents	Asthmagen, any	HMW, any	LMW, any	Cleaning agents
Never asthma (reference)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Adult-onset asthma, four dimensions of asthma control								
Lung function (FEV_1 < 80%)								
No	1.1 [0.9-1.5]	1.2 [0.9-1.6]	1.1 [0.8-1.5]	1.3 [0.9-2.0]	**1.3 [1.0-1.6]**	**1.3 [1.0-1.8]**	**1.3 [1.0-1.7]**	**1.7 [1.2-2.4]**
Yes	1.3 [0.7-2.5]	0.9 [0.4-2.4]	1.0 [0.5-2.4]	1.1 [0.4-3.3]	1.6 [0.9-2.8]	1.5 [0.7-3.1]	1.3 [0.6-2.5]	1.6 [0.7-3.7]
Symptoms#, in the past 3 months								
No	1.1 [0.8-1.5]	1.2 [0.8-1.7]	0.9 [0.6-1.4]	1.1 [0.7-1.9]	1.2 [0.9-1.7]	1.3 [0.9-1.8]	1.2 [0.8-1.6]	**1.5 [1.0-2.2]**
Yes	1.1 [0.8-1.5]	1.1 [0.7-1.7]	1.2 [0.8-1.8]	1.4 [0.8-2.3]	**1.3 [1.0-1.7]**	1.4 [0.9-2.0]	**1.4 [1.0-1.9]**	**1.8 [1.2-2.6]**
Exacerbations#, in the past 12 months								
No	1.0 [0.8-1.3]	1.0 [0.7-1.4]	1.0 [0.7-1.4]	1.1 [0.8-1.7]	1.2 [1.0-1.5]	1.2 [0.9-1.5]	1.2 [0.9-1.6]	**1.5 [1.1-2.1]**
Yes	**2.4 [1.2-4.9]**	**3.5 [1.6-7.6]**	1.5 [0.6-3.8]	**3.0 [1.1-7.9]**	**1.8 [1.0-3.3]**	**2.8 [1.5-5.4]**	1.5 [0.7-3.1]	**2.7 [1.2-5.8]**
Activity limitations#, in the past 12 months								
No	1.1 [0.9-1.5]	1.1 [0.8-1.5]	1.1 [0.8-1.6]	1.3 [0.8-1.9]	**1.3 [1.0-1.6]**	1.2 [0.9-1.7]	**1.3 [1.0-1.7]**	**1.6 [1.1-2.2]**
Yes	1.0 [0.6-1.6]	1.3 [0.7-2.2]	0.8 [0.4-1.5]	1.2 [0.6-2.4]	1.2 [0.8-1.8]	1.5 [0.9-2.4]	1.1 [0.7-1.8]	**1.8 [1.0-3.0]**

Adjusted for age, sex, smoking habits, areas (random effect); reference: participants with 'never asthma'

* Participants exposed to asthmagens were compared to non-exposed participants (participants exposed to *a priori* 'non-asthmagenic' agents excluded). A: asthmagens; HMW: high molecular weight agents; LMW: low molecular weight agents; C: cleaning agents

Symptoms: diurnal symptoms ≥ 1/week or nocturnal symptoms or asthma attack in past 3 months;

Exacerbations: asthma, shortness of breath or wheezing had caused hospital/emergency admissions in past 12 months, or oral steroids were used on short courses or continuously in past 12 months;

Activity limitations: activity limitation at work or in other activities in past 12 months

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